REMARKS

Upon entry of this amendment, claims 2, 5 and 17-21 will be canceled without prejudice or disclaimer of the subject matter recited therein; claims 1, 3, 4, 7, 10-, 11 and 16 will be amended; and claims 22-28 will be added. Accordingly, claims 1-4, 6-16 and 22-28 will be pending. Claims 1 and 3 are independent claims.

Applicant notes that in order to advance prosecution of the application, and without expressing any agreement or acquiescence with the rejections of record, independent claims 1-3 have been amended to further define the stabilizing agent. Moreover, claims 22-28 have been added directed to methods for preparing lyophilized preparations. Additionally, clarifying amendments have been made throughout the claims.

The specification has been amended to correct the Japanese publication number in accordance with remainder of the description the Japanese publication in the specification and examples.

Accordingly, no prohibited new matter should be considered to be introduced by the present amendment.

Reconsideration and allowance of the application are respectfully requested.

Claim Of Priority

The Office Action acknowledges the claim of foreign priority and receipt of the certified copy of the priority document. The Office Action contends that since an

English translation of the priority application has not been filed the effective filing date of this application is the International Filling Date of May 31, 2000.

In contrast to this indication, Applicant submits that the application has a priority date of the Japanese application which only need be established if needed to overcome a reference. In the instant situation, it does not appear to be necessary to submit an English translation of the priority application to antedate any documents. However, to advance prosecution of the application, and to address this issue raised in the Office Action, Applicant is submitting herewith a verified English translation of priority Japanese Application No. 11-151768, filed May 31, 1999.

Consideration Of Information Disclosure Statements

Applicant expresses appreciation for the inclusion with the Office Action of a copy of the initialed Form PTO-1449, whereby the Examiner's consideration of Applicant's Information Disclosure Statements filed February 28, 2002, March 27, 2002 and February 27, 2004 is record.

Applicant notes that the Examiner has crossed through a number of documents on the Forms PTO-1449 or indicated only abstract considered.

Applicant submits that concise English-language explanations of the relevance of the cited documents were included in the Information Disclosure Statements in accordance with Patent and Trademark Office practice. This included English copies of the International Search Report and the International Preliminary Examination Report, citation

and discussion of documents in the specification, submission of English family members and/or English abstracts.

MPEP §609.04(a) states (emphasis added):

> Each information disclosure statement must further include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information listed that is not in the English language. Submission of an English language abstract of a reference may fulfill the requirement for a concise explanation. Where the information listed is not in the English language, but was cited in a search report or other action by a foreign patent office in a counterpart foreign application, the requirement for a concise explanation of relevance can be satisfied by submitting an English-language version of the search report or action which indicates the degree of relevance found by the foreign office. This may be an explanation of which portion of the reference is particularly relevant, to which claims it applies, or merely an "X", "Y", or "A" indication on a search report.

Furthermore, if the Applicant meets these requirements for a non-English language document then the Examiner must indicate that it has been considered in the same manner as consideration is indicated for information submitted in English. This is clearly stated in MPEP 609.05(b) (emphasis added):

> Information which complies with requirements as discussed in this section but which is in a non-English language will be considered in view of the concise explanation submitted (**>see MPEP § 609.04(a), subsection III.<) and insofar as it is understood on its face, e.g., drawings, chemical formulas, in the same manner that non-English language information in Office search files is considered by examiners in conducting searches. The examiner need not have the information translated unless it appears to be necessary to do so. The examiner will indicate that the non-English language information has been considered in the same manner as consideration is indicated for information submitted in English. The examiner should not require that a translation be filed by applicant. The examiner should not make any comment such as that the non-English language information has only been

> considered to the extent understood, since this fact is inherent. See *Semiconductor Energy Laboratory Co. V. Samsung Electronics Co.*, 204 F.3d 1368, 1377-78, 54 USPQ2d 1001, 1008 (Fed. Cir. 2000) ("[A]s MPEP Section 609C(2) reveals, the examiner's understanding of a foreign reference is generally limited to that which he or she can glean from the applicant's concise statement. Consequently, while the examiner's initials require that we presume that he or she considered the [foreign] reference, this presumption extends only to the examiner's consideration of the brief translated portion and the concise statement.").

Moreover, the Office Action indicates that English language translation of the abstracts of Japanese publications have not been received. However, the abstracts are in English. The Examiner is requested to contact the undersigned by telephone to specifically indicate any documents that are needed, and these documents will be immediately forwarded for the Examiner's review and consideration.

Applicant is therefore submitting additional copies of two of the Forms PTO-1449 listing the documents for the first two filed Information Disclosure Statements. The Examiner is respectfully requested to forward initialed copies of the forms with the next communication from the Patent and Trademark Office.

Still further, Applicant is submitting a Third Supplemental Information Disclosure Statement. The Examiner is also requested to forward an initialed copy of the Form PTO-1449 submitted therewith.

Response To Restriction Requirement

The lack of unity of invention has been maintained the indication of lack of unity of invention. In response, Applicant once again submits that the lack of unity of invention indication is without sufficient basis as the requirement does not address the appropriate rules, including 37 C.F.R. 1.475. However, to advance prosecution of the application, withdrawn non-elected claims 17-21 have been canceled without prejudice to the filing of one or more divisional and/or continuations applications.

Regarding the election of species, Applicant respectfully submits that the requirement for election of species is not appropriate in the instant application. In any event, Applicant is permitting the non-elected species to remain pending subject to rejoinder upon allowance of a generic claim.

Response To Objection

Claims 4-6 are objected to as reciting multiple non-elected species.

In response, Applicant respectfully submits that non-elected species are appropriate in the claims subject to rejoinder upon allowance of a generic claim.

Response To Rejections

The following rejections are set forth in the Office Action.

Claims 1 -9, and 12- 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakamura et al. (hereinafter "Nakamura"), European Patent Application 04561 88A1, published 13 November 1991

Claims 1 and 16 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Nakamura.

Claims 1 - 3, 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Tanaka et al. (hereinafter "Tanaka"), WO 97/02832, published 30 January 1997), as evidenced by Tanaka, U.S. Patent Application Publication 2001/0051604, published 13 December 2001, which is the national stage entry of the PCT application that was published as WO 97/02832.

Claims 1 and 16 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Tanaka.

Claims 1 - 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nakamura in view of Tanaka.

In response, Applicant respectfully submits that Applicant's independent claim 1 is directed to a lyophilized preparation comprising a hepatocyte growth factor, a stabilizing agent comprising arginine, lysine, histidine, glutamine, proline, glutamic acid, or aspartic acid, or a pharmacologically acceptable salt thereof for preventing formation of an aggregate of the hepatocyte growth factor, sodium chloride, and a buffering agent, which is prepared from an aqueous solution containing the hepatocyte growth factor at a concentration lower than 5 mg/mL.

Moreover, Applicant's independent claim 3 is directed to a lyophilized preparation comprising a hepatocyte growth factor, a stabilizing agent comprising arginine, lysine, histidine, glutamine, proline, glutamic acid, or aspartic acid, or a pharmacologically

acceptable salt thereof for preventing formation of an aggregate of the hepatocyte growth factor, sodium chloride, and a buffering agent, which is prepared from an aqueous solution containing the hepatocyte growth factor at a concentration lower than 5 mg/mL and capable of preparing an aqueous solution containing the hepatocyte growth factor at a concentration lower than 5 mg/mL by redissolution.

Still further, dependent claim 22 is directed to a method for preparing the lyophilized preparation according to claim 1 comprising lyophilizing an aqueous solution containing the hepatocyte growth factor, the stabilizing agent for preventing formation of an aggregate of the hepatocyte growth factor, the sodium chloride, and the buffering agent, the aqueous solution containing the hepatocyte growth factor at a concentration lower than 5 mg/mL and having a pH in the range of 5.0 to 6.5.

Applicant respectfully submits that neither of Nakamura or Tanaka, whether taken alone or in combination, teaches or suggests the subject matter recited in Applicant's claims.

Prior to discussing Nakamura and Tanaka, Applicant reminds the Examiner that the problem of the state of art is that aggregate formation was observed during storage when a preparation was produced in the presence of glycine or alanine by lyophilizing an aqueous solution containing HGF at a low concentration, which is desirable for clinical application. The use of amino acid is therefore not sufficient as a stabilizing agent when HGF is lyophilized at a low concentration. In this regard, the Examiner's attention is directed to the to page 3 of Applicant's specification wherein it is disclosed

that HGF is a substance having extremely potent physiological activities, and when used as a medicament, the substance needs to be provided in the clinical filed as a pharmaceutical preparation having a very low concentration. Studies by the inventors of the present invention revealed that, as for the lyophilized HGF (TCF) preparation comprising glycine or alanine described in Japanese Patent Unexamined Publication No. 9-25241, only a little formation of aggregates was observed during storage when the lyophilized preparation was produced from an aqueous solution containing HGF at a high concentration, whilst aggregate formation was observed during storage when a preparation was produced in the presence of glycine or alanine by lyophilizing an aqueous solution containing HGF at a low concentration, which is desirable for clinical application (generally, HGF is contained at a concentration lower than 5 mg/mL, for example, about 2 mg/mL). Accordingly, glycine or alanine described in Japanese Patent Unexamined Publication No. 9-25241 is useful as a stabilizing agent when HGF is lyophilized at a high concentration, however, the amino acid is not sufficient as a stabilizing agent when HGF is lyophilized at a low concentration. It has therefore been desired to develop a method for producing a lyophilized preparation that hardly forms aggregates and has excellent stability in long-term storage by using an aqueous solution containing HGF at a low concentration.

The specific combination of the features of Applicant's claims has the effect to avoid the formation of aggregates. The skilled person could not derive the claimed

subject-matter from the cited prior art, since there is no teaching or suggestion to modify either of Nakamura or Tanaka to arrive at Applicant's recited subject matter.

Nakamura includes a broad disclosure which does not teach or suggest Applicant's recited combination of features as a lyophilized preparation, its manner of production or it use. Nakamura broadly discloses that the therapeutic agents of his invention are generally formed into injections containing HGF solely or combinedly with carriers, etc. known per se. For example, he discloses that injections can be prepared by dissolving HGF in suitable buffers, followed by sterilization by filtration through a filter.

Nakamura further discloses that the therapeutic agents for hepatocirrhosis of the invention may contain other additives such as stabilizers, excipients, dissolution-promotors, adsorption-preventors and antioxidants, and examples thereof include, for example, sugars such as mannitol and glucose, amino acids such as glycine, alanine, lysine and arginine, proteins such as albumin, alcohols such as ethylene glycol and glycerol, hydrophilic polymers such as polyethylene glycol, inorganic salts such as NaCl, organic salts such as sodium citrate, surfactants such as Polysorbate 80 and reducing agents containing sulfur, which may be used alone or in combination. However, there is not teaching or suggestion to combine any ingredients in the manner recited in Applicant's claims.

For example, the Examples discloses in Nakamura include Examples 1 — 5 of freeze dried HGF preparations. However, in examples 1 and 2 the buffer solution has a

pH value of 7.4, while no amino acid is used for stabilization. In examples 3 and 4 the aqueous solution does not contain a buffering agent. Only example 5 discloses lyophilization of HGF with a solution comprising an amino acid (glycine). However, the solution of example 5 is not buffered and does not contain a salt.

Regarding Tanaka, the rejection admits that Tanaka discloses 20 mg/ml HGF rather than a concentration of less than 5 mg/ml. However, the rejection contends that this is a product-by-product limitation, and has not given this feature of the claims patentable weight. Certainly, this is not appropriate as this feature is clearly associated with the structure of Applicant's lyophilized preparation and provides a concentration that is different than that taught or suggested by Tanaka. A disclosure of an aqueous solution to be lyophilized containing either 10 mg/ml or 20 mg/ml, as disclosed in Tanaka, does not provide and teaching or suggestion of to arrive at Applicant's claimed subject matter. Further, Applicant has shown unexpected results with the claimed lower concentrations.

In view of the above, it is respectfully submitted that any combination of the prior art utilized in the rejections of record would not arrive at Applicant's claimed subject matter.

Accordingly, these grounds of rejection are without appropriate basis and should be withdrawn.

CONCLUSION

In view of the foregoing, the Examiner is respectfully requested to reconsider and withdraw the objections and rejections of record, and allow each of the pending claims.

Applicant therefore respectfully requests that an early indication of allowance of the application be indicated by the mailing of the Notices of Allowance and Allowability.

Should the Examiner have any questions regarding this Response, the this application, the Examiner is invited to contact the undersigned at the below-listed telephone number.

Respectfully submitted,
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